REMARKS

Applicant respectfully requests reconsideration and allowance of all pending claims.

I. Status of the Claims

In this Amendment C, claims 1, 8, 11, 13, 14 and 22-24 have been amended, while claim 7 has been canceled and claim 26 has been added. Accordingly, claims 1, 3-6 and 8-26 are now pending.

Claim 1 has been amended to call for the elution of the reverse-phase preparative column using an aqueous acidic solution containing an organic solvent. Support for the amendments to claim 1 may be found, for example, in claim 7 (now canceled). Claims 8, 11, 13, 14 and 22 and 23 have been amended in view of the amendment to claim 1.

Claim 24 has been amended for purposes of clarification, to call for the use of a preparative chromatographic column and a reverse-phase packing material therein, as well as elution with an aqueous acidic solution of an organic solvent. Support for the amendments to claim 24 may be found, for example, in claim 1 and claim 7 (now canceled).

Finally, new claim 26 has been added, which calls for the aqueous acidic solution of an organic solvent in claim 24 to have a pH in the range of from about 2.5 to about 3.5. Support for this claim may be found, for example, in claim 8.

II. Existing 35 U.S.C. 103(a) Rejection

Reconsideration is once again requested of the rejection of claims 1, 3-6 and 8-25 under 35 U.S.C. §103 as being obvious in view of Hofstetter (U.S. Patent No. 4,317,903).

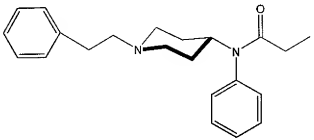
In this regard it is to be noted that, in addition to the comments presented herein, Applicant respectfully reiterates the arguments previously submitted (see, e.g.,

Applicant's Responses dated February 13, 2009 and September 25, 2008). However, in the interests of brevity, those arguments will not be repeated here.

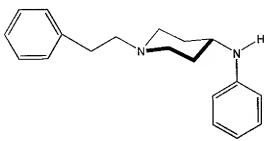
A. The Claimed Subject Matter and Hofstetter

Independent claim 1, from which claims 2-6 and 8-23 depend, as well as independent claim 24, from which claim 25 depends, is directed a process for **recovering pure fentanyl** from an impure preparation of fentanyl containing phenethylpiperaniline, the recovered pure fentanyl having a **phenethylpiperaniline impurity level of less than 0.010 weight percent**. Both of the recited processes comprise, in relevant part, subjecting the impure fentanyl preparation to a reverse-phase high performance preparative liquid column chromatography, wherein (i) the column is **eluted with** a mobile phase comprising an aqueous **acidic solution** containing an organic solvent, and (ii) the loading ratio of column media to fentanyl loaded onto the column is in the range of from about 50 to about 150.

Accordingly, it is to be noted that claims 1 and 24 are **not simply directed** to purification processes. In fact, claims 1 and 24 are also **not simply directed** to a purification process for fentanyl. Rather, these claims are directed to industrial purification processes that comprise separating the desired product, **fentanyl**, from the structurally similar impurity (and common starting material), phenethylpiperaniline, as illustrated below:



Fentanyl



Phenethylpiperaniline

such that the purified fentanyl product has a **concentration of phenethylpiperaniline of less than 0.010 weight percent**. This purification is achieved by reverse-phase high performance preparative liquid chromatography, and more specifically is achieved using

reverse-phase high performance preparative liquid chromatography with the recited **aqueous acidic eluent** and loading ratio.

As previously noted, in contrast to the claimed processes, Hofstetter discloses methods of using a reverse-phase high performance preparative liquid chromatography to obtain a purified preparation of the antibiotic **lincomycin** hydrochloride. The methods generally comprise a number of steps, including: (a) dissolving approximately 450 grams of the starting material (i.e., impure preparation of lincomycin A and lincomycin B) per liter of 30% aqueous methanol; (b) applying the solution to a chromatography column filled with 18 grams of C_{18} bonded phase silica gel per gram of starting material; (c) stripping the remaining lincomycin from the column with 1 bed volume of methanol; (d) concentrating the lincomycin-rich eluate to dryness; (e) crystallizing the lincomycin according to standard crystallization procedure; (f) re-chromatographing the lincomycin B-rich fraction according to the above procedure; (g) concentrating the eluate containing greater than 98% lincomycin B to dryness; and (h) re-dissolving the solids in 3 milliliters of methanol per gram of lincomycin B solids at 40°C and adjusting the pH with concentrated hydrochloric acid to 1.5. Notably, Hofstetter states that the weight ratio recited in step (b) is "near optimum"; that is, Hofstetter states that the weight ratio of silica gel (i.e., the column media) to lincomycin is "near optimum" at 18:1.

B. The Claimed Subject Matter is Not Obvious in view of Hofstetter

In order for the Office to show a *prima facie* case of obviousness, M.P.E.P. §2142 requires a clear articulation of the reasons why the claimed invention would have been obvious. Specifically, to reject a claim based on this rationale, the Office must articulate the following: (1) a finding that there was some teaching, suggestion, or motivation, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings to arrive at each and every limitation of the claimed invention; (2) a finding that there was reasonable expectation of success; and (3) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

Applicant respectfully submits the Office has failed to establish a *prima facie* case of obviousness because each and every element of the claims has not been disclosed or suggested by the cited reference, and/or because there is no motivation to modify the cited reference in order to achieve the claimed subject matter. In support of Applicant's position, Applicant respectfully points out:

(1) As noted above, claims 1 and 24 are **not simply directed** to purification processes. In fact, claims 1 and 24 are also **not simply directed** to a purification process for fentanyl. Rather, these claims are directed to industrial purification processes that comprise separating the desired product, fentanyl, from the structurally similar compound, phenethylpiperaniline, such that the purified fentanyl has a phenethylpiperaniline concentration of **less than 0.010 weight percent**. The presence of **fentanyl** and **phenethylpiperaniline** in the solution being purified, as well as the purity of the recovered fentanyl, are therefore **meaningful limitations that cannot be ignored**. The Office is incorrect in stating that it is simply the "process" that is at issue.

(2) Furthermore, although both **fentanyl** and **lincomycin** are both amines, they have **very different** molecular structures, **as well as** physical properties (e.g., solubilities and pKa values).

(3) The claimed processes also call for elution of the column with an aqueous, **acidic** solution containing an organic solvent. In contrast, Hofstetter is **silent** with respect to the use of such an eluent solution, or even the pH of the eluent solution.

(4) In view of the foregoing, it is clear that Hofstetter **fails to disclose or suggest** each and every element of the claimed processes.

(5) Additionally, and contrary to the Office's assertions, when evaluating the **motivation** of one of ordinary skill in the art to modify the process disclosed by Hofstetter in order to arrive at the claimed processes, **the analysis** (or analogy) **does not and cannot stop** at the conclusion that

the claimed processes and the process of Hofstetter involve the purification of an amine. Rather, **the analysis must be extended to consider the molecules** as a whole, **including** the structure and physical properties (e.g., solubilities and pKa values) the molecules inherently possess. If the analysis truly stopped at the point suggested by the Office, one would conclude that the first disclosure of the use of reverse-phase, high performance preparative liquid column chromatography of **any** amine renders such a process obvious for **all** amines. This is simply not true.

(6) Applicant further submits that the Office continues to give the declaration of the sole inventor, Dr. Enrico Anthony Antonini, **insufficient weight**. The declaration, at least in part, was submitted to address the issue of the motivation of one of ordinary skill in the art. As noted therein, as well as in the Background of the specification, prior to the instantly claimed invention, **precipitation and recrystallization** were typically used for purifying fentanyl. Applicant respectfully submits that **the Office continues to provide an inadequate explanation** regarding why one of ordinary skill in the art, looking to develop a new way of purifying **fentanyl** on an industrial scale, would look to the method disclosed by Hofstetter, which involves the purification of a **very different compound**, both in terms of structure and physical properties. Applicant further submits that one of ordinary skill in the art here would actually look to how existing industrial methods of purification (e.g., precipitation and crystallization) **for fentanyl** could be improved, or would look to other industrial purification methods for compounds having **similar** molecular structure and physical properties.

(7) Finally, Applicant once again points out that the processes of the claimed invention yield a purified fentanyl composition with less than about 0.010 weight percent of phenethylpiperaniline. Applicant submits that if one of ordinary skill in the art merely substituted fentanyl into the process of Hofstetter, as the Office suggests, a purified fentanyl composition with less than about 0.010 weight percent phenethylpiperaniline **would not be**

achieved, due to the differences noted herein, and/or due to the 18:1 weight ratio of column media used by Hofstetter.

In view of the foregoing, Applicant submits the Office has failed to successfully establish a *prima facie* case of obviousness. Applicant further submits, for the reasons set forth above, as well as for the reasons set forth in Applicant's previous submissions, that the Office continues to engage in hindsight reconstruction, using the Applicant's invention as a blueprint, to find the pending claims obvious, which the Federal Circuit has repeatedly ruled against. Accordingly, Applicant submits the present rejection is improper, and therefore request reconsideration and allowance of all pending claims.

III. New 35 U.S.C. 103(a) Rejections

Reconsideration is requested of the rejection of claims 1, 3-6 and 8-25 under 35 U.S.C. §103 as being obvious in view of, individually, Abbott et al. (U.S. Patent No. 4,234,684), Debono et al. (U.S. Patent No. 4,293,489), Hamill et al. (U.S. Patent No. 4,336,333), Fukuda et al. (U.S. Patent No. 4,904,590), and Lazarus et al. (U.S. Patent No. 5,780,589).

A. The Claimed Subject Matter

The relevant details of the claimed subject matter are set forth above and, in the interests of brevity, will not be repeated here.

B. The Claimed Subject Matter is Not Obvious in view of The Cited Art

Applicant respectfully submits the Office has failed to establish a *prima facie* case of obviousness because each and every element of the claims has not been disclosed or suggested by each of the cited references, and/or because there is no motivation to modify each of the cited references in order to achieve the claimed subject matter. In support of Applicant's position, Applicant respectfully points out that, like Hofstetter, each of the cited references fail to disclose or suggest the purification of a compound that has a similar chemical structure, and/or physical properties (e.g., solubility and/or pKa). More specifically, Applicant points point out:

(1) Abbott et al. disclose a method of preparing mycophenolic acid glucoside. This is a compound that is **distinctly different from fentanyl**, including

the fact that it lacks amino, amido and multiple aromatic moieties or substituents, and that it includes a carboxylic acid moiety and an unsaturated carbon-carbon double bond. Furthermore, they are **silent** with respect to the use of an aqueous, **acidic** solution containing an organic solvent to elute the chromatographic column used therein.

(2) Debono et al. disclose a method of preparing derivatives of the antibiotic A30912 factor A. This is a compound that is **distinctly different from fentanyl**, including the fact that it has a significantly higher molecular weight, and includes multiple hydroxyl, carboxyl, amino, amido and heterocyclic moieties or substituents. Furthermore, they are **silent** with respect to the use of an aqueous, **acidic** solution containing an organic solvent to elute the chromatographic column used therein.

(3) Hamill et al. disclose a method of preparing the antibiotic tunicamycin. This is a compound that is **distinctly different from fentanyl**, including the fact that it lacks multiple aromatic moieties or substituents, and that it includes an unsaturated carbon-carbon double bond and multiple hydroxyl, amido and heterocylic moieties or substituents. Furthermore, they are **silent** with respect to the use of an aqueous, **acidic** solution containing an organic solvent to elute the chromatographic column used therein. In fact, Hamill et al. arguably **teach away** from this aspect of the present claims, inasmuch as they disclose the use of a **basic** solution the elute their column.

(4) Fukuda et al. disclose a method of preparing the antibiotic A80915. This is a compound that is **distinctly different from fentanyl**, including the fact that it lacks amino, amido and multiple aromatic moieties or substituents, and that it includes a multiple hydroxyl and chloro moieties or substituents as well as a fused, tricyclic structure. Furthermore, they are **silent** with respect to the use of an aqueous, **acidic** solution containing an organic solvent to elute the chromatographic column used therein.

(5) Finally, Lazarus et al. disclose a method of preparing a particular type of dipeptide. This is a compound that is **distinctly different from fentanyl**, including the fact that it includes a fused, bicyclic ring structure, hydroxyl and primary amino moieties or substituents not present in fentanyl, and additionally at least one of a carboxylic acid, amido, cyano, and ester moieties or substituents not present in fentanyl. Furthermore, they are **silent** with respect to the use of an aqueous, **acidic** solution containing an organic solvent to elute the chromatographic column used therein.

In view of the foregoing, Applicant submits the Office has failed to successfully establish a *prima facie* case of obviousness, because each of the cited references fail to disclose or suggest all of the elements of the claims, and because they simply provide no motivation to modify the disclosure provided therein in order to arrive at the claimed subject matter. Applicant further submits, for the reasons set forth above, that the Office had engaged in hindsight reconstruction, using the Applicant's invention as a blueprint, to find the pending claims obvious, which the Federal Circuit has repeatedly ruled against. Accordingly, Applicant submits the present rejection is improper, and therefore request reconsideration and allowance of all pending claims.

IV. Double Patenting Rejection

Applicants note and thank the Office for their decision to hold the double patenting rejection in abeyance at this time.

CONCLUSION

In view of the foregoing, Applicant respectfully requests favorable reconsideration and allowance of all pending claims.

The Commissioner is hereby authorized to charge Deposit Account 13-1160 for any fees due for the submission of this Response to Final Office Action, and/or for the Request for Continued Examination being filed simultaneously herewith.

Respectfully submitted,

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